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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/809,312	GREENE ET AL.	
	Examiner	Art Unit	
	ROBERT M. KELLY	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,8-11,14,17 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8-11,14,17 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/5/08 and 8/18/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/20/09 has been entered.

Claims 1, 8, 14, 17, and 32 are amended.

Claims 5-7 and 19 have been cancelled.

Claims 1-4, 8-11, 14, 17, and 32 are presently pending and considered.

Notice to Applicant - Non-Compliant Amendments

It is noted that Claims 5-7, 15, 16, and 19 are identified as cancelled, and yet are provided with text, albeit, stricken-through. In addition, it is noted that Claim 4 is identified with "Canceled", however, the text is present. Both of these mistakes make the amendment non-compliant. However, as it is plain from the choice of strike-through versus listing the text, that the striken-through claims (5-7, 15, 16, and 19) are newly cancelled, while Claim 4, even if it was intended to be cancelled, would do no harm to remain under examination at this stage. Hence, the Examiner has noted these errors, and has considered the amendment in the interest of compact prosecution. However, it should be noted that future amendments that are incorrectly labeled, identified, or otherwise improper, will be responded to with a notice of non-compliant amendment.

Claim Status—Cancelled Claims

In light of the cancellation of claims 5-7 and 19, all objections and/or rejections against such claims are rendered moot, and thus, are withdrawn.

Specification

The specification is objected to. Paragraph 0038 recites "In general, neural cells have the potential to differentiate into neural cells (i.e., they are pluripotent)…". Given the context of the sentence, this is an obvious typographical error, as the Artisan would know Applicant means "In general, neural stem cells have the potential to differentiate into neural cells (*i.e.,* they are pluripotent)…".

Appropriate correction is required.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Applicant is advised that should claims 1 or 8 be found allowable, claims 14 or 17, respectively, will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof.

When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims 1 and 14 each claim treating a neural progenitor or neural stem cell with a dominant negative ATF5 to (i) cause differentiation into a differentiated neural cell (Claim 1, preamble) and (ii) induce neural cell differentiation (of the neural/stem progenitor) (Claim 14). Hence, these claims, despite a slight difference in wording, are substantial duplicates.

Claims 8 and 17 depend from Claim 1 and 8, respectively, and have the same terminology, and hence, are each duplicates of each other, in substance, due to the substantially duplicative nature of Claims 1 and 8.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 and 8-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites “the cell”. Such term lacks antecedent basis. It would be remedial to amend the term to recite "the neural stem cell or the neural progenitor cell".

Claims 2-4 and 8-11 are rejected for depending from a rejected base claim.

Claim Rejections - 35 USC § 112 – written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In light of the amendments, the rejections of Claims 1-4, 8-11, 14, 17, and 32 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, are withdrawn.

To wit, Applicant has now amended the claims to encompass only dominant-negative inhibitors.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 8-11, 14, 17, 19 and 32, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's claims are drawn to a generic dominant negative inhibitor of ATF5.

Applicant's dominant negative inhibitor, as is exceedingly evident from the claims, must be dominant negative for ATF5 such that it overrides the activity of ATF5 and causes differentiation of the cell type.

Applicant's specification broadly provides support for any dominant negative inhibitor of ATF5, however, the Examples specifically state that ATF5 does not cause differentiation of cells by forming neurites (paragraph 0174). At best, the evidence is weak, in that in limited tests, Applicant's dominant-negative construct when expressed seemed to have marginal effects in the rate of cell differentiation in a population exposed to the differentiation-inducing agent NGF (FIGURES 2B and 2C), however, such was limited to the first two days, and differentiation was still taking place afterward. The Examiner does not know what to make of this, but it is not considered strong enough evidence, especially given the fact that the sole dominant negative construct did not cause any formation of neurites in the absence of NGF.

Moreover, the Art does not demonstrate dominant negative inhibitors for ATF5 which cause differentiation of neural progenitor or neural stem cells.

Hence, the Artisan would not have understood Applicant to have been in possession of a dominant negative inhibitor of ATF5 which causes such differentiation.

Claim Rejections - 35 USC § 112—new matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In light of the amendment to Claim 32, the rejection of such claim under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn.

To wit, the claim is now limited to eGFP.

Claim Rejections - 35 USC § 112 - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 8-11, 14, 17, and 32 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Dominant Negative Inhibitors of ATF5 Rejection (core to all enablement)

At the core of the newly-proffered rejection, it is found that Applicant's (and the Art's) sole demonstration of a dominant-negative inhibitor of ATF5 is actually not a dominant negative inhibitor of ATF5 and does not cause differentiation of even Applicant's sole embodiment which is demonstrative of dominant-negative effects. However, each of Applicant's claims require the administration of a dominant negative inhibitor of ATF5 to cause such an effect.

To wit, Applicant's specification admits that the sole dominant negative inhibitor demonstrated (i.e., NTAzip-ATF5), when transfected into cells, did not stimulate any neurite outgrowth (paragraph 0174). Applicant's sole demonstration of "dominant negative" activity is found in that the co-expression of the dominant negative inhibitor in cells exposed to NGF

demonstrated a 2-fold increased rate of neurite outgrowth (i.e., the cell population had increased levels of differentiated cells over time such that a rate would determine a 2-fold increased rate of differentiation). However, such does not demonstrate it to be a dominant negative inhibitor. Applicant's data is limited to two time points in ten, and in the end, it would appear that the dominant negative inhibitor did not cause neurite outgrowth without NGF treatment, and yet, NGF causes neurite outgrowth even without ATF. Its difficult to say much more without more data, like affinity constants, stronger time-dependent studies, etc. However, what is clear is that the dominant negative inhibitor had no effect in the absence of NGF, and hence, it would not work in any of the methods provided.

Hence, the Artisan would have to experiment to find an inhibitor which caused neurite outgrowth of neural stem/progenitor cells in the absence of NGF, and further determine if it acted through ATF5. Such is considered undue as it amounts to inventing the claimed subject matter for Applicant.

Further, one other basis of rejection of record remains: transplantation (the scope is clearly described in the official action of 11/19/08, e.g., p. 8).

Still further, a new basis of rejection should be considered to bring the claims to allowability, should Applicant overcome the other bases: the breadth of cells which are encompassed.

These claims are broad for *ex vivo* therapies, as well as the breadth of cells which can be forced into differentiation by ablating the action of ATF5 (and of course, the use of ATF5, already fully addressed above).

eGFP not expressed by a promoter activated in the differentiated cell (Claim 32 – acts as completely non-enabling; Claims 1-4, 8-11, 14-17 eGFP not in a vector transforming the neural stem/progenitor cells, and under control of a promoter which is expressed only in the differentiated cells)

(Claim 32) In short, the method does not require the eGFP to be linked to promoter which is expressed solely in the differentiated cell type, and hence, it would not work, as it is never expressed, even if a dominant negative inhibitor of ATF5 existed.

Hence, the Artisan would have to determine which promoter to utilize in any particular case to have it expressed in the specific differentiated cell type, as well as determine which cell types will respond (below), and which cell types will evolve (below).

Such experimentation is considered undue as it amounts to inventing Applicant's invention for Applicant.

(Claims 1-4, 8-11, and 14-17) In short, Applicant's methods require enablement for a system in which the differentiated neural cells express eGFP, as evidenced by Claim 4. However, the claims do not require administration of a vector encoding eGFP, and the proper operably linked promoter to express the eGFP in the differentiated cells, as exacerbated by Claim 32's evidence that the promoter is not even required, and further, like Claim 32, Artisan would have to determine which promoter to utilize in any particular case to have it expressed in the specific differentiated cell type, as well as determine which cell types will respond (below), and which cell types will evolve (below).

Such experimentation is considered undue as it amounts to inventing Applicant's invention for Applicant.

Ex Vivo Rejection (All claims):

All claims encompass the intended use, taught in the specification, for ex vivo therapy, as evidenced by Claims 8-11 and 17, and the fact that the specification provides for only one use of the derived cells: ex vivo therapy.

The field of stem cell therapy for treating neurodenerative diseases is not very well fleshed out such that the Artisan could reasonably predict that any particular disorder could be treated, and further for any individual with the disorder. Pluchino, et al. (2005) Brain Research Reviews, 48: 211-19 teaches that the science is still in its infancy, with multiple art-recognized problems that must be overcome before applying widespread therapeutic applications of neural stem cell compositions to humans with neurogenerative disease/injury (e.g., p. 215, conclusion). The factors involved in the efficacy of such transplantation methods are not well understood.

In addition, Stanworth, et al. (2001) Clinical Medicine, 1(5): 378-82 teaches there are multiple issues impeding the widespread use of the combination of gene therapy and stem cells, including lack of efficiency of gene transfer and vector design as well as regulatory issues (e.g., p. 381, col. 1, paragraph 3). Thomas, et al. (2003) Nature Reviews Genetics, 4: 346-58 teach that multiple hurdles must be overcome for viral vector administration, inlcuding potential immune response, limited understanding of integration potential into oncogenes, and the ability of animal studies to predict response in humans. Thomas discloses that the human response to viral based therapies are more variable than those observed in animal models and therefore, it is difficult to make solid predictions based on non-human trials (e.g., p. 356, col. 1, paragraph 2). Further, Thomas teaches that the predictability of individual response to inflammatory vectors remains a "substantial challenge" (e.g., Id.).

Further, stem cell therapy for neurodegenerative disease and trauma is not reasonably predictable. The lack of predictability is found in the areas of: efficacy of stem cell delivery to the area of degeneration, persistence in the disease area and proliferation control. Pluchino notes that while totipotent ES cells have been used in transplants, there is no consistent data on the use of ES cell derived, lineage restricted, neural cells (e.g., p. 213, paragraph 3). Further, Pluchino teaches that recent ES cell transplant studies have resulted in formation of heterologous tissue and teratomas at the site of administration (e.g., Id., paragraph 4). Further ES cell related issues include optimal sources of cells for transplant, optimal administration methods for the cells, and determination of differation state and persistence of the transplanted cells in the area to be treated (e.g., Id., p. 212, col. 1, last paragraph). Still further, it is not reasonably predictable that the properties of transplanted neural cells would remain after transplantation as *in vivo* animal models in which even adult differentiated cells displayed altered pathways of differentiation when they are transplanted into diseased animals versus healthy animals (e.g., pp. 213-14, paragraph bridging). Efficacy of such stem cell pharmaceuticals is not reasonably predictable due to possible migration or dispersion of the stem cells to or from the degenerated area, especially in some diseases like Alzheimer's (e.g., Id.). In addition, any neural stem cells that are transplanted into a patient would be under the influence of a myriad of growth factors, hormones, and other molecules that would influence their differentiation fate and efficacy of treatment in any individual case (e.g., p. 214, last paragraph). Further, Gerlach, et al. (2002) Journal of Neurology, 249(Suppl. 3): III/33-35 cites multiple problems related to stem cell therapies including variation in therapeutic effect, side effects and the difficulty in using fetal or stem cell tissue (e.g., p. 34, col. 1, paragraph 3). The problems also lie in the unregulated proliferative

potential of neural stem cells. Clinical evidence has shown that uncontrolled neural progenitor cells growth and differentiation in the brain of Parkinson's disease patients may result in death. In light of this, Gerlach suggests therapeutic implant of cells differentiated *in vivo* prior to transplant, but also cite the need to eliminate the possibility of uncontrolled proliferation and further suggest long-term preliminary studies in animals prior to widespread administration of such cells in human patients (e.g., p. 34, col. 2, paragraph 3).

Still further, the specific *in vivo* differenation and *ex vivo* therapies are argued against for several reasons, essentially amounting to the fact that for any specific disorder, specific cells are destroyed, degenerated, and affected, and the transplanted or differentiated cells must differentiate into or be transplanted into the tissue in the specific amounts and ratios to replace the specific cell type(s) that have been affected. Still further, these cells must actually replace the diseased cells in terms of not only presence, but also function.

To wit, while discussing stromal cells, the issues bought up by Bartley herein are applicable to the instant case, as the progenitors must be able to differentiate in the correct proportions and replace the damaged tissue. To wit, Bartley, et al. (2003) Expert Opin. Biol. Ther., 3(4): 541-49 provides an overview for stem cell therapy for cerebral palsy (TITLE) which will suffice to delineate some of the problems with such therapies. Bartley only recognizes that two methods of administration appear to be feasible for treatment of cerebral palsy, those of intravenous or direct injection (p. 542, col. 1, paragraph 4), neither of which, as will be shown below, is yet to be reasonably predictive of delivering enough cells to the site of action. In stating such, Bartley also recognizes that it is not reasonably predictable that any therapy can be effected with such cells injected into the vasculature, due to the permeability of the blood-brain

barrier (Id.). Hence, on top of only two methods of administration being feasible to produce therapeutic effects, Bartley also recognizes that it is not necessarily reasonably predictable that vascular administration would produce a therapeutic effect. Next, with palsy, as with many diseases of the central nervous systems, patients have differing effects with regard to amounts of grey or white matter (and specific cell types and ratios of cell types) being lost, and therefore, the type of cell used to effect such therapy must be able to reasonably predictably differentiate into each of the cell types in the correct proportions (p. 542, col. 1, paragraph 5), and, in fact, it is not even reasonably predictable which or whether both need to be replaced in any particular instance of the disorder (Id.). Therefore, even for any subset of diseases of the CNS, it is not reasonably predictable which cells to replace in the first place, much less whether marrow stromal cells can do so for each cell type and in the correct proportions. Moreover, mere replacement of certain forms of cells may not effect a disease, as in palsy, where Bartley demonstrates that it is not reasonably predictable that replacement of myelin, without replacement of the axons themselves, would facilitate any functional improvement (p. 542, col. 2, paragraph 2).

Bartley also indicates that the choice of cell type, stage of differentiation, and derivation are critical issues, indicating the specific stem cell may not be efficacious for any particular form of palsy, much less any disorder of the central nervous system (Id., paragraph 3). Further, for the cell type used in Bartley (MSCs), Bartley also provides numerous lines of evidence to indicate that marrow stromal cells can differentiate into various tissues and that such **may** be able to occur *in vivo* (p. 544, col. 1), but also there exists conflicting data (Id., paragraph 2). With regard to method of administration, Bartley again emphasizes that it would seem unlikely that intravenous injection would get enough cells to the site to effect treatment (p. 544, paragraph

bridging columns). Further, Bartley questions the use of undifferentiated cells, and indicates that it is not reasonably predictable yet, requiring further experimentation, to determine the state of differentiation which should be applied in any particular treatment (p. 544, last paragraph). Furthermore, it is noted that even when these cell differentiate in some fashion, it is not clear whether such is the source of the therapeutic effect, or whether recovery is mediated by some other substance elaborated by the implanted cells (p. 545, col. 1, paragraph 2), and therefore, Applicant's requirement that the cells differentiate may actually not cause any therapeutic effect at all. Moreover, other results indicate that improvements in function may not be linked to the implantation of the cells themselves (Id., col. 2, paragraph 1), making the results suspect for any therapy associated with stromal cell therapy to the brain. Also, Bartley, even when a finding seems positive, indicates the need for further confirmation of the information before the data can be fully accepted (Id.).

Bartley also indicates that immune reactions may occur, which may be detrimental (Id., paragraph 2). This can further be interpreted that such immune reactions may kill any transplanted cells before they could effect therapy.

In conclusion, Bartley indicates that while the data is encouraging, extensive experimentation is still required before human treatment will be feasible (p. 545, col. 2, paragraph 2; p. 546, col. 1). Clearly, Bartley is indicating that somatic cell therapy with stromal cells is not reasonably predictable of therapy in humans at this point, which is after Applicant's filing date.

Still further, Savitz, et al. (2003) Journal of Cardiovascular Nursing, 18(1): 57-61, suggests that another disorder, stroke recovery, cannot be reasonably predicted with progenitor

cells, as it is not known if the cells would actually replace the damaged cells, and in the proper proportions as well as the grafts would remain viable or die, which would require "**extensive investigation**" (e.g., p. 60, paragraph bridging columns). Further, extensive investigation would be required to yield useful data to draw practical information and make it reasonably predictalbe (last sentence).

Still further, in the case of Parkinson's disease, once the processes are lost that cross from the substantia nigra to the striatum, it would appear that the replacement with new processes is not reasonably predictable, even when living cells are present in the proper context, and encouraged to sprout new processes across the border (e.g., Bjorklund, et al. (2000) Brain Res., 886: 82-98, article in general) and further, even with the data presently available for treatment, the models utilized are not recognized by the Artisan to be reasonably predictive of treatment (e.g., INTRODUCTION, p. 83, col. 1, first full paragraph; pp. 89-90, paragraph bridging).

In essence, it is clear that any particular transplant would require the correct cells in the correct proportions to be transferred to acheive a therapeutic effect in any disorder, but the amounts and proportions are not reasonably predictable, even when the evidence appears to suggest particular porportions/amounts, as it appears to not reasonably predictable in any case. Still further, simply inducing random differentiation, as Applicant's examples show (induction of neurites) does not reasonably predict replacement of the damaged cell(s). Such replacements may not occur at all, or may occur to thwart normal cells in the damaged tissue, thereby not reasonably predicting any therapy. Still further, with damaged CNS tissue, it would not be reasonably predictable that any particular form of administration would allow the cells to reach the site of action due to the blood brain barrier, and it is further noted that other forms of

administration to the peripheral nervous system are also known to be thwarted by the body's own systems, e.g., the liver would remove the cells from the blood system.

Applicant's specification and examples demonstrate the *in vitro* differentiation of neural progenitor cells, but fail to demonstrate any specific therapy, by transplant or *in vivo* administrations, and as such fails to overcome the various aspects considered non-enabled. **Still further, Applicant's only demonstration is one of neurite genesis, and does not demonstrate any particular cell type.**

Hence, even if the Artisan determined a dominant negative inhibitor that worked, the Artisan would have to experiment with routes of administration for the various disorders, determine if the various administrations cause replacement of the damaged/affected cells in the proper proportions to treat the disease, and also determine which neuronal stem/progenitor cells would form the correct populations of cell types to produce the desired effect for any disease. Such is considered undue as it amounts to inventing Applicant's claimed breadth for Applicant.

Hence, the claims are not enabled for that scope provided in the initial form paragraphs.

Neural Stem and Progenitor Cells, as well as Derived Neuronal Cell Type Rejection

Applicant's claims encompass promoting differentiation of any neural stem cell or neural progenitor cell into a differentiated neural cell, and inducing any neural stem cell or neural progenitor cell to differentiate into anything. Such is necessarily broad for the cell type, and cell types which can be formed from each.

Applicant's specification provides broad description of an intent to utilize any neural cell or neural progenitor or neural stem cell to produce any other cell type, including other non-completely differentiated cells, and the use of non-neuronal cells which can be forced to

differentiate into any specific cell type or be induced to differentiate. However, the description is lacking in which cells are utilized to produce which cell types when ATF5 is inhibited.

The examples demonstrate that NGF exposure causes PC12 cells and VZ cells of early telencephalon to differentiate to some extent by producing neurites (semi-formed processes indicative of neurons. However, beyond that, description is lacking as to the types of cells which are formed such that the Artisan would know which differentiated cell types are formed and in which proportions.

From this, at best, there appears to be a link between NGF and ATF5.

However, Kalcheim, et al. (1986) Developmental Biology, 116(2): 451-66 (ABSTRACT ONLY PROVED), make clear that stem cells of the neural crest appear to not to depend on NGF to continue proliferating and surviving (ABSTRACT). Hence, because the critical link is not there of an influence on differentiation by NGF, it is also apparent that the link is not implied for ATF5.

Still further, Cassiman, et al. (2001) Hepatology, 33(1): 148-58 demonstrates that several receptors, and hence, several cascades are involved in stem cells of the liver, the other tissue demonstrated to have ATF5 by Applicant (e.g., ABSTRACT). Hence, the Artisan would question whether the ATF5 pathway is influenced in these cells. This is emphasized by Trim, et al. (2000) American Journal of Pathology, 156(4): 1235-43, wherein it is specifically found that these Hepatic Stellate Cells undergo apoptosis in the presence of NGF (e.g., TITLE). Hence, the Artisan would not even predict for any particular cell which expresses an NGF receptor that such necessarily equates to ATF5 repression of differentiation in the absence of NGF. What is even more clear is that these cells, while having related receptor compositions, do not undergo normal

ontogeny to form neural cells of any specific type. Therefore, in this case, if a dominant negative inhibitor were found that worked, and it were applied to the stem cell, no neuronal cell would form, but the cells would die, if ATF5 is even involved, otherwise, no effect would be found.

Still further, Gratch, et al. (2002) Developmental Biology, 83-94 have demonstrated that noggin and chordin appear to induce differentiation of ES cells to neural phenotype, while BMP-4 appears to inhibit such differentiation (e.g., ABSTRACT). However, BMP is not NGF, and ATF5 is not shown as a generic inhibitor of all pathways. In fact, if it were, it would necessarily shut down all cell responses, and the cell would die.

What all this demonstrates is that any specific pathway of development depends on the stage and specific receptors and pathways in play at that stage of development. Hence, to extrapolate from Applicant's limited showing, and relying heavily on cancer cells (e.g., PC12 cells, as well as several other cancer cells), is not something the Artisan would do. It is clear that NGF is not involved in neural crest cell development into neurons, that NGF kills hepatic stem cells, and that neural development of other cells which are neural stem cells can rely on distinct metabolic pathways. Hence, it is clear, even given Applicant's showing, that the breadth of stem cells and progenitor cells (including neural stem cells and neural progenitor cells), would still not be reasonably predicted to be inhibited in their differentiation due to the simple exposure to increased levels of ATF5. Further, it is demonstrated that any specific cell type, under any specific conditions do not necessarily make any particular neural cell. For Example, noggin and chordin have distinct lineage commitment activities for ES cells (e.g., Gratch, TITLE).

Therefore, the Artisan would have to further experiment to find out which cell types could be forced to differentiate, which cell types they form, and which disorders could be treated

by such cells in the proper proportions. Such is considered undue as it amounts to inventing Applicant's claimed subject matter for Applicant.

Conclusion

For the reasons given above, the Artisan would have to perform undue experimentation to enable Applicant's claimed inventions.

Response to Argument – Enablement

Applicant's argument of 4/20/09 has been fully considered but is not found persuasive.

Applicant argues that the claims have been amended to being directed to *in vivo* differentiation and hence, the rejection is overcome.

Such is not persuasive. Claims 8-11 and 17 are specifically evidence that the scope includes *ex vivo* transplantation of the derived cells. Still further, the new bases of rejection must now be addressed.

Claim Rejections - 35 USC § 102 - anticipation

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

In light of the amendments, the rejections of Claims 1-4, 8-11, 14, and 17 under 35 U.S.C. 102(b) as being anticipated by Angelastro, et al., (2000) Proceedings of the National of Academy of Science, USA, 276(15): 12190-121200 are withdrawn.

To wit, the claims are limited to dominant negative inhibitors of ATF5 that cause differentiation of the neural stem/progenitor cells.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT M. KELLY whose telephone number is (571)272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert M Kelly/
Primary Examiner, Art Unit 1633